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Improving the predictive capability of Framingham Risk Score for risk of myocardial infarction based on coronary artery calcium score in healthy Singaporeans

Ching Yee Ivory Yeo[1], BSc, John Carson Allen Jr[2] , PhD, Weiting Huang[3], MBBS, MMed, Wei Ying Tan[4], BS(BBA), MS(MTech), Siew Ching Kong[3], BSc, Khung Keong Yeo[3], MBBS

[1]Duke-NUS Medical School, [2]Centre for Quantitative Medicine, Duke-NUS Medical School, [3]Department of Cardiology, National Heart Centre Singapore, [4]Institute of Data Science, National University of Singapore, Singapore

Correspondence: Ms Yeo Ching Yee Ivory, Medical Student, Duke-NUS Medical School, 8 College Road, Singapore 169857. ivoryyeo@u.duke.nus.edu

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ABSTRACT

Introduction: Cardiovascular disease emerged as the top cause of deaths and disability in Singapore in 2018, contributing extensively to the local healthcare burden. Primary prevention identifies at-risk individuals for the swift implementation of prevention or corrective measures. This has been traditionally done using the Singapore-adapted Framingham Risk Score (SG FRS). However, its most recent recalibration was done more than a decade ago. Recent changes in patient demographics and risk factors have undermined the accuracy of SG FRS, and the rising popularity of wearable health metrics have given rise to new data types with the potential to improve risk prediction.

Methods: In healthy Singaporeans enrolled in the SingHEART study (in the absence of any clinical outcomes), we investigated potential improvements in the SG FRS to predict myocardial infarction risk based on high/low classifications of the Agatston score (surrogate outcome). Logistic regression, receiver operating characteristic and net reclassification index (NRI) analyses were conducted.

Results: We demonstrated a significant improvement in the area under curve (AUC) of the SG FRS *(AUC=0.641)* after recalibration and incorporation of additional variables (fasting glucose and wearable-derived activity levels) *(AUC=0.774) ($p<0.001$).* SG FRS++ significantly increases accuracy in risk prediction *(NRI=0.219, p=0.00254).*

Conclusion: We suggest that existing Singapore CVD risk prediction guidelines be updated to improve risk prediction accuracy. Recalibrating existing risk functions and utilising wearable metrics which provide a large pool of objective health data can help improve existing risk prediction tools. Lastly, activity levels and pre-diabetic state are important factors to consider for CHD risk stratification methods, especially in low-risk individuals.

Keywords: coronary calcium, lifestyle, primary prevention, risk stratification, wearable health metric

INTRODUCTION

In Singapore, cardiovascular disease (CVD) was the top cause of all deaths by broad cause and top cause of early death and disability, accounting for 30.2% of all deaths in 2018 with 17 deaths daily due to CVD.[1,2] Primary prevention of CVD and coronary artery disease (CAD) requires identification of at-risk individuals, allowing for swift implementation of effective preventive or corrective measures, including lifestyle changes. This has traditionally been done using risk scores such as the Framingham Risk Score (FRS) which is calculated using a combination of cardiovascular risk markers and clinical characteristics such as age and gender.[3]

Traditional risk scoring systems such as the FRS predict risk by assessing a variety of parameters routinely obtained from simple clinical assessment and blood tests. However, the traditional FRS has some disadvantages. The original Framingham risk function was developed based on the Framingham Heart study of white middle-class individuals, hence additional recalibration of the risk function to improve predictive accuracy in other populations is required. The FRS does not take into account well-known CVD risk factors such as diet and physical activity level which provide important discriminatory value, especially in healthy cohorts. FRS predicts only 60% to 65% of myocardial infarctions (MI) or sudden cardiac deaths, however in most individuals the first presentation of disease is a MACE, such as MI, or even death.[4]

While there is a recalibrated Framingham risk function that provides a more accurate estimate of CVD risk for the Singapore population (SG FRS), the study was done more than a decade ago, and coefficients are likely to be outdated today. However, it remains the most precise estimate of absolute CVD risk for the Singapore population that is currently available and is still widely used in clinical practice. There is therefore a pressing need to recalibrate and improve the prediction capability of the SG FRS to identify asymptomatic individuals who are

at high risk of CVD and MACE in order to implement preventive strategies in our Singaporean population.

In healthy Singaporeans enrolled in the SingHEART study and using baseline data, we proposed to investigate potential improvements in the performance of the Singapore-adapted Framingham Risk Score for 10-year risk of hard coronary heart disease (SG FRS) as a clinical tool to predict risk of myocardial infarction (MI) based on the high/low calcification classifications of the Agatston coronary artery calcium score (CACS) as a surrogate outcome in the absence of any clinical outcomes.

While it would be ideal to develop an improved risk model for MI in our Singaporean cohort using incident MACE in our SingHEART cohort, the SingHEART study is the first population-based study conducted in Asia combining conventional clinical information with the latest technology in genomics, imaging, wearable data and analytics, and was only recently established in 2015. Given our study population of 663 volunteers, an extensive time horizon would be required to accrue enough events in the form of MI or other MACE and is beyond the scope of our study.

Agatston CACS is a highly specific feature of coronary atherosclerosis and reflects coronary age. Several large long-term observational studies produced evidence of a strong association between CACS and MACE in asymptomatic individuals and showed that CACS improves statistical risk restratification.[5,6] Relative risk of MI also increases with higher CACS and CACS has been widely used to guide lipid therapy for primary prevention of CVD.[7] As an excellent predictor of MI, the Agatston high/low CACS classification was therefore chosen as a surrogate outcome for MI in our study.

METHODS

The SingHEART/Biobank study was established at the NHCS to characterise normal reference values for various cardiovascular and metabolic disease-related markers in Singaporeans. The study aims to combine conventional clinical information with the latest technology in genomics, imaging, wearable data and analytics to assess pre-existing risk markers and identify new risk markers in cardiovascular disease, especially in our local context, and to characterise cardiovascular health in Asians.[8]

Volunteer recruitment was carried out as described previously.[8] Normal volunteers were enrolled into this study using a protocol and written informed consent form approved by the SingHealth Centralised Institutional Review Board (ref: 2015/2601). A secondary written informed consent for this sub-study was required, and only those completing the secondary informed consent were enrolled in the study. The volunteers underwent comprehensive profiling in the following areas: (1) activity tracking using the Fitbit Charge HR wearable sensor, (2) lifestyle questionnaire, (3) cardiac imaging consisting of coronary magnetic resonance (MRI) and coronary non-contrast CT imaging, (4) fasting lipid and glucose panel, (5) assessment of clinical parameters (e.g. HR, blood pressure, waist circumference, BMI). A total of 663 volunteers were included in this study after evaluation for completeness of activity tracking data (details below). Inclusion criteria were as follows:

1. Aged between 30 and 69 years.
2. No personal medical history of myocardial infarction (MI), coronary artery disease (CAD), peripheral arterial disease, diabetes mellitus (DM), psychiatric illness, asthma, or chronic lung disease and chronic infective disease.
3. No personal medical history of cardiomyopathies.

Data was stored behind a hospital firewall at NHCS in accordance with the PDPA and other applicable laws. Data was anonymised and processed prior to being received by the author who then performed the data processing and statistical analysis.

Socioeconomic status, diet, smoking, alcohol consumption, traditional Chinese medicine (TCM) use and activity history were obtained as described previously.[8]

Volunteers were issued a Fitbit Charge HR wearable activity tracker to be worn over 5 days. However, as the first and last days of the study tended to be partial days, the average yield for each study was 3.24 days and 3.16 days of complete tracking in males and females respectively. Complete tracking was defined as ≥ 20 hours with steps and HR data (Data for each subject were obtained as described previously.[8])

To determine data completeness, presence of HR data was used as an indicator that the subject was wearing the device. HR values were merged with the steps table by the time points. Days with ≥ 20 valid hours were considered to be complete. Days with no step data were excluded.

To determine Resting_HR, the average HR value for timepoints which met the following criteria was calculated: (1) had ≤ 100 steps take place within a 15-minute interval and (2) had a valid HR value. To determine DailySteps, the average sum of steps that took place in data-complete days was calculated for each subject. DailySteps was used as a measure of wearable-derived physical activity for this study.

Clinical and laboratory parameters were collected as described previously.[8]

The SG FRS was used in this study as several studies have shown that the US Framingham function over predicts cardiovascular risk when applied to Asian populations, especially Chinese.[9,10]

The SG FRS was calculated according to the Ministry of Health (MOH) Clinical Practice Guidelines on Screening of Cardiovascular Disease and Risk Factors. The recalibrated

SG FRS is used in the MOH Clinical Practice Guidelines on Lipids 2006. The risk scores in the Singapore MOH guidelines were derived from the Framingham-based NCEP ATP III 10-Year Risk Score Tables, which were modified to take into account Singapore cardiovascular epidemiological data.

The following clinical markers were considered for calculation of the SG FRS in this study: SBP, TotalChol and HDL. Other parameters considered were BMI, WC, DBP, LDL, TG, FBG, Urea, Alkaline Phosphatase and GGT.

Moderately or severely elevated coronary artery calcium score was defined as an Agatston Score $\geq 75^{th}$ percentile for each individual according to age- and gender-adjusted thresholds.[11]

For both SG FRS and US FRS, a score of ≤ 10 is considered 'low' risk, a score between 10 to 20 is considered as 'intermediate' risk, and a score > 20 is considered 'high' risk. In this study, the cohort consisted of healthy individuals resulted in a very small percentage of 'high-risk' individuals. The 'intermediate' and 'high' risk groups were therefore merged to form an 'InterHigh' risk group to be compared to the 'low' risk group in the subsequent analysis.

Coronary MRI and coronary non-contrast CT were performed as described previously.[8]

For the primary analysis, 663 out of 800 volunteers were included, as only those of age $\geq$ 30 years underwent coronary CT scan for calcium scoring. For the analysis including wearable metric data, 443 of 800 volunteers were included based on availability of data downloaded from the Fitbit API and after excluding missing and invalid data according to the criteria stated in the "Activity Tracking" section.

All statistical analyses were performed using Statistical Analysis System (SAS) University Edition. Intermediate data processing and data cleaning was done in Python language. Variables with > 20% missing values were excluded from analysis.

Logistic regression analysis was used to assess multiple potential risk factors and identify a subset of 'best' independent predictors. Variables investigated included clinical parameters and lifestyle factors such as physical activity not accounted for in the SG FRS. These predictors were used to improve the SG FRS to predict risk of MI based on the Agatston CACS high/low classification. Analyses were performed using both continuous and categorical forms of the SG FRS. Continuous SG FRS scores (Risk) are reflected by an integer percentage risk FRS, while categorical SG FRS groups (RiskClass) are reflected as low- (≤10% continuous SG FRS) and intermediate/high-risk (>10% continuous SG FRS) groups.

Receiver operator characteristic (ROC) analysis was conducted to investigate predictive capabilities of the risk models for MI. ROC curves based on the SG FRS were compared to SG FRS+ and SG FRS++ alone (Fig. 1-2). The SG FRS, SG FRS+ and SG FRS++ were compared to check for significant differences between ROC curves. Recalibration of the SG FRS was done using multivariable logistic regression to predict a binary outcome of high/low Agatston. We also evaluated whether the SG FRS++ new risk model provided meaningful improvements in accuracy of risk classification. The net reclassification index (NRI) and two-sided 95% confidence interval were calculated.[12] To determine NRI, we used cut points of 10% for 10-year risk of CHD when using SG FRS, and defined a threshold for high or low MI risk with the new SG FRS++ model determined from the ROC analysis. All reported *p*-values were two sided and statistically significant at $p<0.05$.

RESULTS

Summary statistics of the cohort containing 663 volunteers are shown in Table Ia and Ib, grouped by gender and Agatston CACS category respectively.

Table Ia compares baseline characteristics between males and females. Males had significantly higher BMI, waist circumference, blood pressure, lipids, fasting glucose,

Agatston and FRS compared to females. Wearable-derived activity levels did not differ significantly between males and females.

Table Ib compares baseline characteristics between the high Agatston CACS group and low Agatston CACS group. Volunteers with high Agatston CACS had significantly higher FRS, blood pressure, total cholesterol, fasting glucose, ABPM derived pulse rate and wearable-derived resting heart rate. Higher heart rates potentially reflect poorer heart rate control. We also note that volunteers with high Agatston CACS showed higher activity levels (daily step counts).

Cohort median ages were 48.9 and 50.2 years in females and males respectively (range 30-69 years old) with a preponderance of females (366/663, 55.2%). Of note, there were no females in the intermediate/high-risk FRS category.

Table II shows the results of the univariate logistic regression analysis performed including SG FRS to identify potential predictors of high Agatston as a surrogate outcome of MI.

In the multivariable analysis, DBP (OR=1.026; 95% CI 1.002-1.050), LDL (OR=1.458; 95% CI 1.016-2.092), Glucose (OR=1.805, 95% CI 1.098-2.966), wearable derived *ln*DailySteps (OR=2.561, 95% CI 1.168-5.612) and RestingHR (OR=1.051, 95% CI 1.002, 1.102) were identified as independent predictors for high Agatston, with statistical significance ($p<0.05$).

In Fig. 1, we compared the AUC for the improved SG FRS+ which included selected variables (Glucose, DBP, *ln*DailySteps, RestingHR) with the basal AUC for SG FRS.

Our results show that the additional variables such as fasting blood glucose, DBP, LDL, and wearable-derived metrics such as *ln*DailySteps and RestingHR improved the SG FRS for both the categorical and continuous risk scores, increased the predictive value of both models (SG FRS+) in our healthy cohort.

Although the SG FRS+ showed improved predictive capability for high Agatston, it remains that the original SG FRS may not be reflective of the present Singapore population. This is in view that the SG FRS model was developed from an old study on a different cohort, and coefficients for the original variables such as age, gender, SBP, total cholesterol and HDL cholesterol may be outdated.

To recalibrate the coefficients of the original SG FRS while still incorporating additional variables with predictive capability to generate the final risk model (SG FRS++), we repeated the above logistic regression and ROC analyses using the variables in the SG FRS as basal variables rather than the computed SG FRS score as the basal AUC (Fig. 2). This allowed investigation of potential interactions between the newly incorporated variables such as DBP and Glucose with the original variables such as age, gender, SBP, total cholesterol and HDL cholesterol, recalibrating the coefficients of the original variables in the SG FRS.

Although the statistically optimal cutoff was defined as p=0.15 with a Youden index of 0.40 (blue dashed line in Fig. 2), we lowered the predictive probability threshold to p=0.10 (black dashed line in Fig. 2), increasing the NPV from 92.6% to 94.2%. This decision was made considering the clinical implications of erroneously classifying a high-risk individual to the low-risk group.

In Fig. 3, we compared the ROC curves of the SG FRS, SG FRS+ and the SG FRS++. Of note, we observed a statistically significant increase in AUC between SG FRS (AUC=0.641) and SG FRS++ (AUC=0.774) (p<0.001), and between SG FRS+ (AUC=0.708) and SG FRS++ (AUC=0.774) (p=0.0049). However, no statistically significant difference in AUC between SG FRS and SG FRS+ was found (p=0.1216).

To assess the generalisability of our recalibrated and improved SG FRS model, a 10-fold cross validation analysis was conducted (Fig. 4).

Similar to the analysis using the computed SG FRS as the basal AUC, although the statistically optimal cutoff was defined as p=0.15 with a Youden index of 0.40 (blue dashed line in Fig. 4), we lowered the predictive probability threshold to p=0.07 (black dashed line in Fig. 4), increasing the NPV from 91.1% to 93.1% for the 10-fold cross-validated recalibrated and improved SG FRS++ model.

Reclassification for volunteers with and without events are summarised in Table III. For 50 volunteers experiencing events (high Agatston as surrogate outcome), classification improved using the SG FRS++ model which was recalibrated to incorporate additional variables, and for 2 volunteers it became worse, resulting in a significant net reclassification gain of 0.219. The calculated NRI (95% CI) was 0.219 (0.109, 0.329) (p=0.00254).

DISCUSSION

The primary aim of this study was to identify variables that are good predictors of high Agatston CACS—and hence MI risk—to augment the SG FRS. Fasting blood glucose, diastolic blood pressure (DBP), wearable-derived resting heart rate (RHR) and wearable-derived average daily steps (*ln*DailySteps) were found to be independent predictors of CHD risk. The improved model (SG FRS+) using basal SG FRS and incorporating the above variables resulted in a predictive model with a significantly improved predictive value (AUC=0.708) for high Agatston and MI risk compared to the original SG FRS (Fig. 1). Ultimately, the final model (SG FRS++) involved recalibration of the existing SG FRS variables and the incorporation of the above variables resulting in further improvement of predictive capability (AUC=0.774) of high Agatston (hence MI risk) compared to the SG FRS+ (Fig. 2).

In our analysis, we made the decision to lower the predictive probability threshold to attain a higher NPV in our SG FRS++ model. This decision was made considering the clinical

implications of erroneously classifying a high-risk individual to the low-risk group. The benefit of this decision is a lowered risk of adverse outcomes due to additional follow-up consultations and implementation of primary prevention strategies.

We report a further improvement in predictive capability of the SG FRS after incorporation of variables shortlisted from the SingHEART database. Even though DBP and LDL are known to correlate with existing FRS variables such as SBP, we show that they still serve as independent predictors of CHD risk even after recalibration of the original SG FRS.

The ideal risk stratification model should have a good balance of complexity and utility, and adding variables to a risk stratification model increases the complexity of the clinical tool. It is necessary to examine the clinical and public health implications involved, hence further studies to investigate the additional burden of obtaining the extra variables are needed. If the cost is low, it might be worth including these additional variables in the risk prediction model. Therefore, we suggest that additional variables may be incorporated into CHD risk stratification for healthy cohorts, as they provide the additional discriminative value to group these individual into low- or high-risk groups.

The traditional Framingham risk function only accounts for the absence or presence of a formal diagnosis of DM, but fails to take into account pre-diabetic individuals with impaired glucose tolerance or impaired fasting glucose (IFG). These early metabolic abnormalities in glucose regulation such as insulin resistance and impaired insulin secretion are associated with CVMD and higher risk of development of DM. IFG has predictive value for all-cause mortality and CVD risk independently of other CVD risk factors which are traditionally used to calculate the SG FRS. Non-diabetic individuals have different risk levels for CHD which is not accounted for in the SG FRS. Studies have shown that the relationship between glucose levels and CVD risk extends below the diabetic threshold.[13] Using a risk prediction method which includes glucose as a risk factor has also been shown to improve the risk prediction for

cardiovascular mortality.[14] Similarly in our cohort, we identified fasting glucose as a predictor for high Agatston, which improves the predictive capability of existing SG FRS for CHD and MI risk.

Our results have several important implications. First, we show that information on the pre-diabetic state – such as fasting glucose levels – provides important discriminative value to the risk stratification of a healthy, non-diabetic cohort. Pre-diabetic individuals in healthy cohorts can then be offered more aggressive interventions such as lifestyle intervention to treat their hyperglycaemia and other risk factors. Early identification of the pre-diabetic state and implementation of intervention strategies are important steps in the progress on the War on Diabetes, which was launched in MOH Singapore in 2016 in response to the significant health and societal burden posed by DM.

The SG FRS has been used to identify Singaporeans at high cardiovascular risk for preventive care and disease management. When used in a healthy Singaporean cohort as in this study, incorporating additional variables can provide important discriminative value to improve SG FRS as a clinical tool (AUC=0.641). Our results showed that the recalibrated and improved function (SG FRS++) showed greater predictive capability for risk of MI compared to the SG FRS+, raising the AUC from 0.704 to 0.774. Even after the 10-fold cross validation, the SG FRS++ AUC still maintained useful predictive capability (AUC=0.721).

We showed that the recalibrated and improved SG FRS++ significantly improved risk prediction accuracy and identified high-risk individuals who were previously classified as low-risk (NRI = 0.219). Identifying such high-risk individuals at improved accuracy is an important strategy for primary prevention of CVD. Currently, the SG FRS is used to calculate cardiovascular risk to guide important clinical management, such as the initiation of statin therapy for high-risk individuals. We suggest that individuals with high SG FRS++ risk scores

can be advised to start empirical medical treatment, more aggressive treatment of their underlying risk factors, or to undergo additional testing for CVD.

Sedentary lifestyle is associated with higher risk of cardiovascular and metabolic disease (CVMD), and obtaining patient history on their physical activity is important for risk stratification. Although self-reporting measures via questionnaires are useful, wearable technology measuring actual motion of the body rather than participant recollections and perceptions of activity which are subject to bias, can provide more objective and accurate measures of activity levels.[15]

Coupled with the recent advancements in wearable technology, personal fitness tracking is becoming increasingly affordable and used by the population.[16] Our results show that wearable-derived activity level data improved the discriminatory ability of existing CVD risk stratification methods. However, this large pool of continuously logged objective wearable health data is not actively used for risk stratification purposes by clinicians or researchers. To increase accuracy of risk stratification based on lifestyle and activity patterns, we suggest adopting the use of wearable metric data for monitoring activity levels and other health metrics of patients in the community setting.

Based on NRI and its components, we conclude that our new model SG FRS++, which includes recalibration and additional variables, improved classification for a net of 21.9% in our Singapore cohort. This improvement is comparable or even superior to the NRI found in other similar studies – albeit in Western cohorts – which investigated the incorporation of biomarkers to augment the FRS, with NRI of 20.7 and 12.1 reported respectively.[12,17]

Our findings suggest that existing guidelines by the MOH Singapore which utilise the SG FRS for CHD risk prediction need to be updated to improve our risk classification methods. There are several reasons for this. First, patient demographics and underlying risk factors have changed since the last risk function recalibration. In addition, new data types such as wearable-

derived metrics are now available and have been shown to improve existing risk prediction models. Finally, we have identified the pre-diabetic state, which has not been considered in previous risk functions, as an important risk factor for CHD and MACE.

The present study has some limitations. First, high/low classifications of Agatston CACS is only a surrogate outcome for MI. Ideally, actual MI outcome data should be used to build the predictive model. Using Agatston as a surrogate outcome is less ideal, but still necessary at this point to identify potential predictors of MI risk and to guide clinical practice before outcome data is available in the future. Second, there were no females allocated to the high-risk group according to the SG FRS. Third, our study population consists mostly of Chinese (93.8%), which is an overrepresentation of the proportion of Chinese in the Singaporean population (75%).[18] With underrepresentation of other ethnic groups such as Indians, Malays and others in our study cohort, we were unable to accurately determine ethnic differences. Lastly, even though this study showed that short duration of tracking (3 days) was sufficient to observe associations, perhaps longer tracking periods would prove to be even more useful to improve power on detecting associations between activity and calcium scores.

In conclusion, updating the SG FRS is necessary to account for demographic changes and risk factors in the Singapore population which contributes to higher CHD risk. This can be done via recalibration and incorporation of additional variables which impart additional discriminative value but at the cost of increased complexity. By adopting the use of wearable health metric data in risk stratification, access can be obtained to a large pool of objective and continuously-logged health data obtained from patients in the community setting. To strike a balance between complexity and utility of risk prediction tools, we suggest that additional variables such as fasting glucose be considered for CHD risk stratification in healthy cohorts. Further studies on the utility of proactive screening in healthy cohorts, and follow up studies

using data from the SingHEART database to re-evaluate the improved Framingham risk model using actual outcome data are warranted.

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TABLES

Table Ia – Summary statistics of volunteers, grouped by gender

Characteristic	Total (N=663)	Female (N=366, 55.2%)	Male (N=297, 44.8%)	P-value*
Age, years	49.4 ± 9.15	48.9 ± 9.12	50.2 ± 9.15	0.0726
Height, m	1.65 ± 0.08	1.59 ± 0.06	1.71 ± 0.06	**<0.001**
Weight, kg	64.3 ± 12.5	58.1 ± 9.59	71.8 ± 11.4	**<0.001**
BMI, kg/m^2	23.6 ± 3.7	23.0 ± 3.74	24.5 ± 3.47	**<0.001**
<17				
17-22				
≥23				
Waist circumference, cm	83.0 ± 11.0	79.1 ± 10.3	87.8 ± 9.76	**<0.001**
Systolic blood pressure (SBP), mmHg	127.9 ± 17.4	123.8 ± 17.9	132.8 ± 15.3	**<0.001**
Diastolic blood pressure (DBP), mmHg	78.2 ± 13.0	73.8 ± 13.2	83.5 ± 10.6	**<0.001**
Total cholesterol, mmol/L	5.44 ± 0.94	5.42 ± 0.931	5.46 ± 0.962	0.5985
High-density lipoprotein cholesterol (HDL), mmol/L	1.49 ± 0.34	1.60 ± 0.322	1.37 ± 0.309	**<0.001**
Low-density lipoprotein cholesterol (LDL), mmol/L	3.42 ± 0.81	3.36 ± 0.791	3.48 ± 0.837	0.0700
Triglycerides, mmol/L	1.18 ± 0.68	1.03 ± 0.561	1.38 ± 0.766	**<0.001**
Fasting blood glucose, mmol/L	5.32 ± 0.63	5.21 ± 0.529	5.44 ± 0.722	**<0.001**
GGT, mmol/L	28.3 ± 18.9	23.42 ± 16.4	34.3 ± 20.1	**<0.001**
Alkaline Phosphatase, mmol/L	70.6 ± 18.4	69.6 ± 19.6	71.8 ± 16.8	0.1300
Urea, mmol/L	4.44 ± 1.12	4.18 ± 1.09	4.77 ± 1.08	**<0.001**
Pulse rate, bpm				
ABPM_HR	71.9 ± 11.8	72.0 ± 11.0	71.8 ± 12.7	0.8530
ECG_HR	63.8 ± 9.62	63.9 ± 9.2	63.7 ± 10.1	0.8094
Smoking Pack Years	1.42 ± 5.83	0.59 ± 3.47	2.44 ± 7.70	**<0.001**
LVMass	75.8 ± 21.2	63.46 ± 13.1	90.7 ± 19.4	**<0.001**
LVEF, %	61.6 ± 6.43	63.0 ± 5.75	59.9 ± 6.81	**<0.001**
LVEDV	121.3 ± 24.1	109.7 ± 17.0	135.7 ± 23.7	**<0.001**
Aorta Forward Flow	71.1 ± 13.0	66.1 ± 10.2	77.3 ± 13.3	**<0.001**
Fitbit-derived DailySteps (N)	11185 ± 4520 (370)	11080 ± 4679 (218)	11336 ± 4292 (152)	0.5923
Fitbit-derived *ln*DailySteps	9.24 ± 0.40	9.23 ± 0.42	9.27 ± 0.38	0.3796
Fitbit-derived Resting_HR (N)	68.0 ± 6.53 (370)	68.1 ± 6.58 (218)	67.9 ± 6.48 (152)	0.7697
Valid_Days, days (N)	3.20 ± 1.48	3.16 ± 1.45 (234)	3.24 ± 1.52 (166)	0.6012
Agatston coronary artery calcium score (CACS)	47.79 ± 208.01	14.3 ± 56.7	89.0 ± 299.5	**<0.001**
Low risk (N, %)	(366, 47.96)	(318, 47.96)	(240, 36.20)	
High risk (N, %)	(296, 44.80)	(48, 7.24)	(57, 8.60)	
Singapore adapted Framingham Risk Score	2.60 ± 3.39	0.95 ± 1.23	4.62 ± 4.03	**<0.001**

(SG FRS)				
Low risk (N, %)	(366, 47.96)	(366, 55.20)	(264, 39.82)	
Intermediate and High risk (N, %)	(296, 44.80)	(0, 0.00)	(33, 4.98)	
US Framingham Risk Score (US FRS)	3.61 ± 4.64	1.04 ± 1.39	6.78 ± 5.24	**<0.001**
Low risk (N, %)	(366, 47.96)	(366, 55.20)	(250, 37.71)	
Intermediate and High risk (N, %)	(296, 44.80)	(0, 0.00)	(47, 7.09)	

Table Ia: Summary statistics of volunteers, grouped by gender. *Female (n=366, 55.2%) Male (n=297, 44.8%). For continuous variables, Student t-test was used, whereas categorical values were evaluated using the chi-squared test. Abbreviations: ABPM_HR, ambulatory blood pressure monitor derived heart rate; BMI, body mass index; DailySteps, wearable derived average daily steps; DBP, diastolic blood pressure; ECG_HR, electrocardiogram heart rate; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; lnDailySteps, logarithm of DailySteps; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMass, Left ventricular mass; Resting_HR, wearable derived resting heart rate; Risk, Framingham risk score for 10 year risk of hard coronary heart disease (adjusted for the Singapore population); SBP, systolic blood pressure; Valid_Days, average valid days of data tracking using wearable derived data. Non parametric test (Wilcoxon Rank-Sum test) and normalizing transformation of variables were all consistent with the t-test results. All p-values were two sided and statistically significant for p<0.05.*

Table Ib – Summary statistics of volunteers, grouped by Agatston coronary artery calcium score

Characteristic	Total (N=663)	Low Agatston (N=558, 84.2%)	High Agatston (N=105, 15.8%)	P-value*
Age, years	49.4 ± 9.15	48.7 ± 9.19	53.5 ± 7.8	**<0.001**
Height, m	1.65 ± 0.08	1.64 ± 0.08	1.65 ± 0.09	0.3858
Weight, kg	64.3 ± 12.5	64.1 ± 12.2	65.0 ± 13.8	0.5124
BMI, kg/m^2	23.6 ± 3.7	23.6 ± 3.68	23.7 ± 3.79	0.9682
<17				
17-22				
≥23				
Waist circumference, cm	83.0 ± 11.0	83.1 ± 11.1	82.7 ± 10.4	0.7628
Systolic blood pressure (SBP), mmHg	127.9 ± 17.4	126.3 ± 16.9	136.4 ± 84.4	**<0.001**
Diastolic blood pressure (DBP), mmHg	78.2 ± 13.0	77.0 ± 12.7	73.1 ± 12.3	**<0.001**
Total cholesterol, mmol/L	5.44 ± 0.94	5.38 ± 0.94	5.74 ± 0.91	**<0.001**
High-density lipoprotein cholesterol (HDL), mmol/L	1.49 ± 0.34	1.48 ± 0.33	1.54 ± 0.35	0.0942
Low-density lipoprotein cholesterol (LDL), mmol/L	3.42 ± 0.81	3.37 ± 0.82	3.64 ± 0.76	**0.0017**
Triglycerides, mmol/L	1.18 ± 0.68	1.17 ± 0.68	1.26 ± 0.68	0.2223
Fasting blood glucose, mmol/L	5.32 ± 0.63	5.28 ± 0.57	5.53 ± 0.86	**0.0051**
GGT, mmol/L	28.3 ± 18.9	28.0 ± 19.2	29.7 ± 17.0	0.3908
Alkaline Phosphatase, mmol/L	70.6 ± 18.4	70.33 ± 18.8	72.0 ± 16.6	0.3943
Urea, mmol/L	4.44 ± 1.12	4.40 ± 1.12	4.66 ± 1.13	**0.0351**
Pulse rate, bpm				
ABPM_HR	71.9 ± 11.8	71.7 ± 11.7	73.1 ± 12.3	0.2560
ECG_HR	63.8 ± 9.62	63.5 ± 9.57	65.7 ± 9.68	**0.0332**
Smoking Pack Years	1.42 ± 5.83	1.24 ± 5.46	2.35 ± 7.45	0.1486
LVMass	75.8 ± 21.2	74.3 ± 20.1	83.9 ± 24.8	**<0.001**
LVEF, %	61.6 ± 6.43	61.5 ± 6.29	62.1 ± 7.12	0.4339

LVEDV	121.3 ± 24.1	121.5 ± 23.6	120.5 ± 26.6	0.6916
Aorta Forward Flow	71.1 ± 13.0	71.4 ± 12.9	69.2 ± 13.1	0.1013
Fitbit-derived DailySteps (N)	11185 ± 4520	10956 ± 4512 (306)	12281 ± 4431 (64)	**0.0328**
Fitbit-derived *ln*DailySteps	9.24 ± 0.40	9.22 ± 0.41	9.36 ± 0.34	**0.0138**
Fitbit-derived Resting_HR (N)	68.0 ± 6.53	67.6 ± 6.43 (306)	70.0 ± 6.70 (64)	**0.0068**
Valid_Days, days (N)	3.20 ± 1.48	3.18 ± 1.50 (331)	3.29 ± 1.36 (69)	0.5588
Agatston coronary artery calcium score (CACS) Females (N, %) Males (N, %)	47.79 ± 208.01 (366, 47.96) (296, 44.80)	8.59 ± 42.9 (318, 47.96) (240, 36.20)	256.1 ± 462.1 (48, 7.24) (57, 8.60)	**<0.001**
Singapore adapted Framingham Risk Score (SG FRS) Females (N, %) Males (N, %)	2.60 ± 3.39 (366, 47.96) (296, 44.80)	2.44 ± 3.40	3.44 ± 3.20	**0.0056**
US Framingham Risk Score (US FRS) Females (N, %) Males (N, %)	3.61 ± 4.64 (366, 47.96) (296, 44.80)	3.36 ± 4.58	4.95 ± 4.74	**0.0012**

Table Ib: Summary statistics of volunteers, grouped by Agatston coronary artery calcium score*. Low Agatston (n=558, 84.2%) – High Agatston (n=105, 15.8%). For continuous variables, Student t-test was used, whereas categorical values were evaluated using the chi-squared test. Abbreviations: ABPM_HR, ambulatory blood pressure monitor derived heart rate; BMI, body mass index; DailySteps, wearable derived average daily steps; ECG_HR, electrocardiogram heart rate; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; lnDailySteps, logarithm of DailySteps; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMass, Left ventricular mass; Resting_HR, wearable derived resting heart rate; Risk, Framingham risk score for 10 year risk of hard coronary heart disease (adjusted for the Singapore population); Valid_Days, average valid days of data tracking using wearable derived data. Non parametric test (Wilcoxon Rank-Sum test) and normalizing transformation of variables were all consistent with the t-test results. All p-values were two sided and statistically significant for p<0.05.*

Table II – Univariate and multivariable logistic regression analysis to identify potential predictors for high Agatston score

Variable	**Univariate Odds Ratio (95% CI)**	**P value**	**Multivariable Adj. Odds Ratio (95% CI) [2]**	**P-value**
Singapore adapted Framingham Risk Score (Risk)	1.076 (1.020, 1.135)	0.0069		
Singapore adapted Framingham Risk Class (RiskClass)		0.7054		
Low risk	1.00		1.00	--
Intermediate and high risk	1.192 (0.480, 2.962)		0.642 (0.161, 2.555)	0.5297
Gender		0.0339		
Female	1.00			
Male	1.573 (1.035, 2.392)			
Age	1.064 (1.038, 1.091)	<0.001		
Systolic blood pressure (SBP)	1.033 (1.021, 1.046)	<0.001		
Diastolic blood pressure (DBP)	1.046 (1.029, 1.065)	<0.001	1.026 (1.002, 1.050)	**0.0356**
Total cholesterol	1.477 (1.192, 1.831)	<0.001		
High-density lipoprotein (HDL) cholesterol	1.678 (0.914, 3.078)	0.0948		
Low-density lipoprotein (LDL) cholesterol	1.477 (1.154, 1.892)	0.0020	1.458 (1.016, 2.092)	**0.0407**
Triglycerides	1.190 (0.899, 1.575)	0.2235		

Fasting blood glucose	1.657 (1.229, 2.233)	0.0009	1.805 (1.098, 2.966)	**0.0198**
Urea	1.213 (1.013, 1.453)	0.0359		
ECG_HR	1.023 (1.002, 1.045)	0.0338		
LVMass	1.020 (1.010, 1.030)	<0.001		
Fitbit-derived DailySteps	1.000 (1.000, 1.000)	0.0352		
Fitbit-derived *ln*DailySteps	2.412 (1.190, 4.890)	0.0146	2.561 (1.168, 5.612)	**0.0188**
Fitbit-derived Resting_HR	1.058 (1.015, 1.103)	0.0076	1.051 (1.002, 1.102)	**0.0414**
Marital status		0.1288		
Married	1.00			
Separated/divorced	2.052 (0.774, 5.439)			
Single	0.603 (0.318, 1.146)			
Widowed	2.052 (0.392, 10.750)			
Coffee consumption		0.2208		
Never/rarely	1.00			
< 1 cup a week	1.664 (0.685, 4.042)			
≥ 1 cup a week but ≤ 1 cup a day	1.808 (1.031, 3.172)			
Others	1.571 (0.873, 2.829)			
Tea consumption in cups per day				
Chinese tea	1.293 (0.998, 1.675)	0.0515		
Green tea	1.234 (0.966, 1.577)	0.0930		
Tea consumption				
English tea weekly		0.2324		
Never/rarely	1.00			
< 1 cup a week	0.368 (0.090, 1.500)			
≥ 1 cup a week but ≤ 1 cup a day	0.278 (0.060, 1.290)			
Others	0.588 (0.124, 2.785)			
Chinese tea weekly		0.1618		
Never/rarely	1.00			
< 1 cup a week	0.657 (0.341, 1.265)			
≥ 1 cup a week but ≤ 1 cup a day	1.126 (0.656, 1.933)			
Others	2.186 (0.872, 5.480)			
Green tea weekly		0.1442		
Never/rarely	1.00			
< 1 cup a week	0.879 (0.482, 1.603)			
≥ 1 cup a week but ≤ 1 cup a day	0.920 (0.538, 1.572)			
Others	2.175 (1.049, 4.506)			
Smoking in Pack Years	1.027 (0.997, 1.058)	0.0801		

Table II – *Logistic regression model for myocardial infarction (high Agatston score as a surrogate) of Singapore adapted Framingham Risk Score and Singapore adapted Framingham Risk Class to identify independent predictors of high Agatston coronary artery calcium score as surrogate of myocardial infarction risk. Abbreviations: DailySteps, wearable derived average daily steps; ECG_HR, electrocardiogram heart rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; lnDailySteps, logarithm of DailySteps; LVMass, Left ventricular mass; Resting_HR, wearable derived resting heart rate; Risk, Framingham risk score for 10 year risk of hard coronary heart disease (adjusted for the Singapore population); RiskClass, Framingham risk class for 10 year risk of hard coronary heart disease (adjusted for the Singapore population). All p-values were two sided and statistically significant for p<0.05.*

[1] The multivariable analysis included only variables significant at $p<0.25$ in univariate analysis, which are variables included in this table. Other variables which were omitted from multivariable analysis were those already used for the calculation of the Singapore adapted Framingham Risk Score which include: Age, Systolic blood pressure, Gender, High-density lipoprotein (HDL) cholesterol and Total cholesterol.

[2] Additional variables investigated were not significant at p≥0.25 were the following: Height, Weight, Body mass index, Waist circumference, Gamma-glutamyl transferase, Alkaline phosphatase, ABPM derived heart rate, Race, Alcohol consumption in units, Alcohol consumption weekly in units, Alcohol consumption (Y/N), Alcohol consumption, Coffee consumption in cups per day, English tea consumption in cups per day, Diet (Fruit servings daily, vegetable servings daily), Smoking status and Traditional Chinese Medicine use (Y/N).

[3] Area under ROC curve (95% CI) for multivariable model using categorical FRS (RiskClass) was 0.7310 (0.6670, 0.7949). 10-fold cross-validated area under ROC curve (95% CI) 0.6940 (0.6268, 0.7611).

[4] Area under ROC curve (95% CI) for multivariable model using continuous SG FRS (Risk) was 0.7077 (0.6387, 0.7767). 10-fold cross-validated area under ROC curve (95% CI) was 0.6734 (0.6014, 0.7455).

[5] Area under ROC curve (95% CI) for multivariable model using continuous SG FRS (Risk) with recalibration of original FRS variables was 0.7742 (0.7138, 0.8346). 10-fold cross-validated area under ROC curve (95% CI) was 0.7210 (0.6543, 0.7876).

Table III – Cross tabulation tables of reclassification of volunteers using the old model SG FRS and new model SG FRS++, grouped by events and non-events using Agatston coronary artery calcium score as a surrogate outcome

Events (High Agatston) (n=105)

Old Model (SG FRS)	**New Model (SG FRS++)**		
	Low	**High**	Column Total
Low	49	50	99
InterHigh	2	4	6
Row Total	51	54	105

50 events correctly reclassified to high risk
2 events incorrectly reclassified to low risk
53 events not reclassified

Net of 45.71% (48/105) of events correctly reclassified by the new model SG FRS++

Non-events (Low Agatston) (n=558)

Old Model (SG FRS)	**New Model (SG FRS++)**		
	Low	**High**	Column Total
Low	381	150	531
InterHigh	17	10	27
Row Total	398	160	558

150 non-events incorrectly reclassified to high risk
17 non-events correctly reclassified to low risk
391 non-events not reclassified

Net of 23.84% (133/558) of non-events incorrectly reclassified by the new model SG FRS++

NRI = $[(\frac{50}{105})-(\frac{2}{105})] + [(\frac{17}{558})-(\frac{150}{558})]$ = 21.88%

Table III *– Net Reclassification Index (NRI) was done to determine if the new model SG FRS++ provides improvements in risk prediction. The NRI (95% CI) was 0.219 (0.109, 0.329), indicating a statistically significant net improvement in accuracy of risk classification by the new model SG FRS++ (p=0.00254).*

Table IV – Cross tabulation tables of reclassification of volunteers using the old model SG FRS and intermediate model SG FRS+, grouped by events and non-events using Agatston coronary artery calcium score as a surrogate outcome

Events (High Agatston) (n=105)

Old Model (SG FRS)	**Intermediate Model (SG FRS+)**		
	Low	**High**	Column Total
Low	45	54	99
InterHigh	2	4	6
Row Total	47	58	105

54 events correctly reclassified to high risk
2 events incorrectly reclassified to low risk
49 events not reclassified

Net of 49.52% (52/105) of events correctly reclassified by the intermediate model SG FRS+

Non-events (Low Agatston) (n=558)

Old Model (SG FRS)	**Intermediate Model (SG FRS+)**		
	Low	**High**	Column Total
Low	341	190	531
InterHigh	15	12	27
Row Total	356	202	558

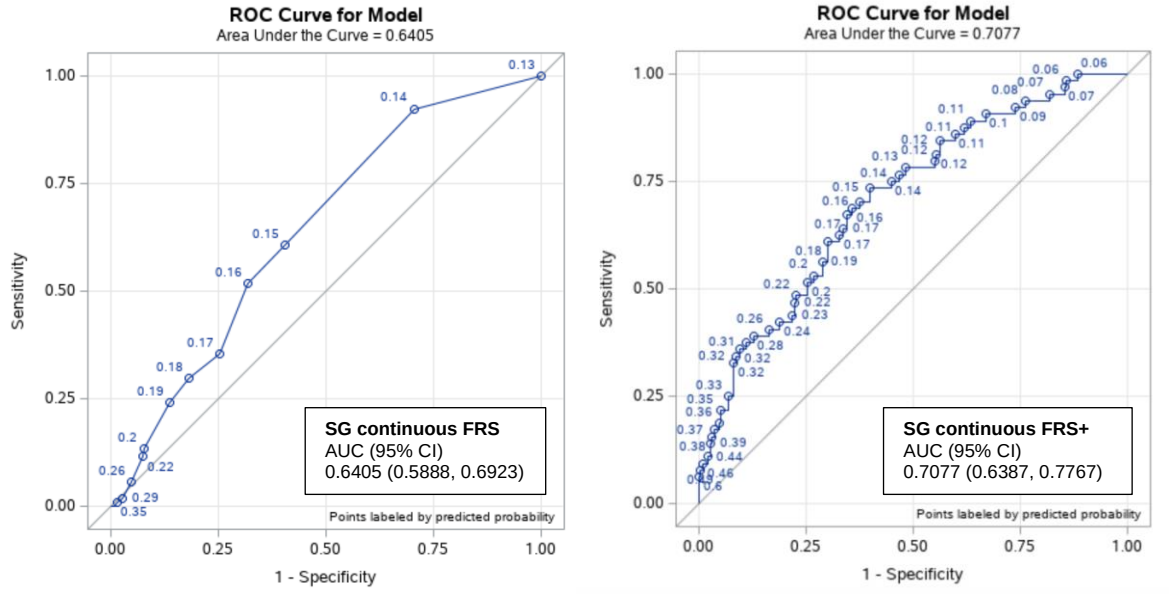
190 non-events incorrectly reclassified to high risk
15 non-events correctly reclassified to low risk
353 non-events not reclassified

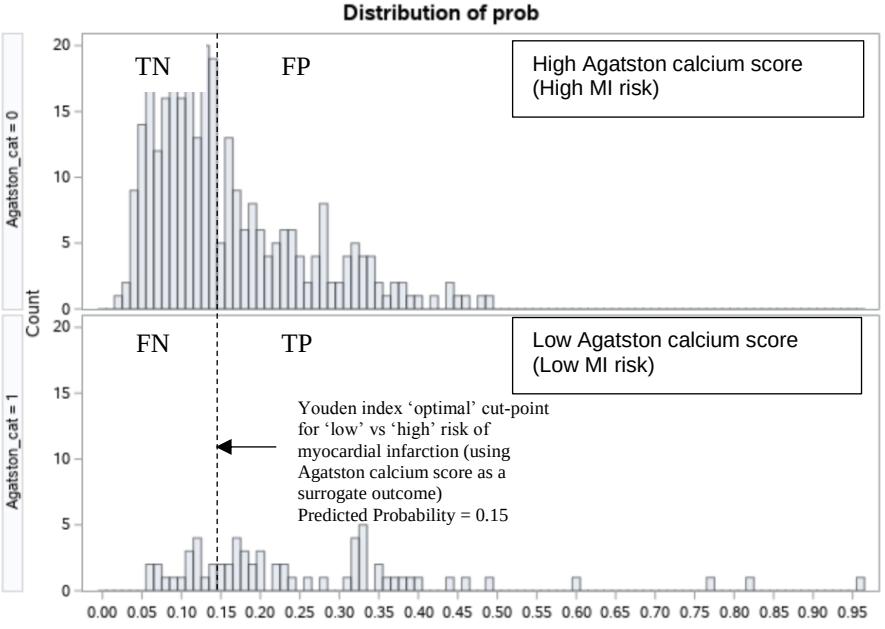
Net of 31.36% (175/558) of non-events incorrectly reclassified by the intermediate model SG FRS+

NRI = $[(\frac{54}{105})-(\frac{2}{105})] + [(\frac{15}{558})-(\frac{190}{558})]$ = 18.16%

Table IV *– Net Reclassification Index (NRI) was done to determine if the intermediate model SG FRS+ provides improvements in risk prediction. The NRI (95% CI) was 0.182 (0.0703, 0.2929), indicating a statistically significant net improvement in accuracy of risk classification by the new model SG FRS+ (p=0.0165).*

FIGURES





Predicted probability of high calcium score and risk of myocardial infarction

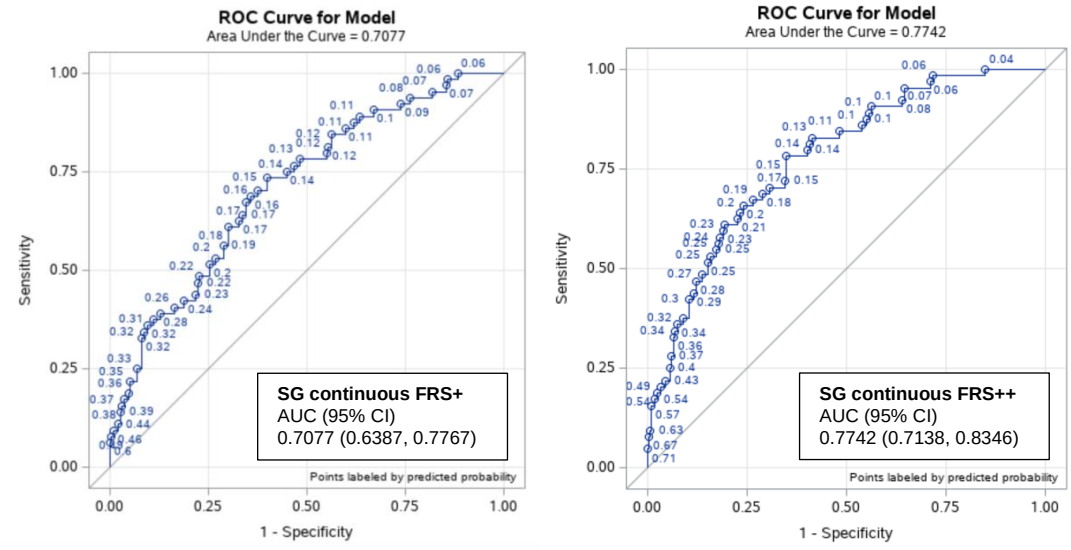
Logistic regression myocardial infarction linear predictor:

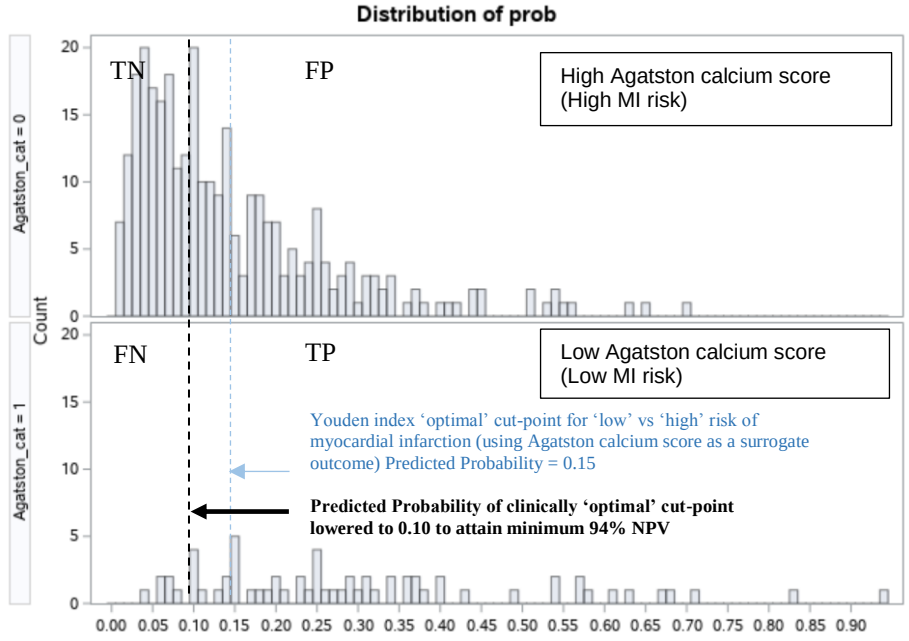
y = - 19.3011 + 0.0257·Risk + 0.6147·Glucose + 0.0265·DBP + 1.0200·*ln*DailySteps + 0.0400·Resting_HR

Predicted probability of myocardial infarction: $p = e^y/(1 + e^y)$

Predicted probability Agatston ≥ 75th percentile	Sensitivity	Specificity	PPV	NPV	Youden Index
0.13	0.77976	0.49132	0.24725	0.91236	0.27108
0.14	0.74405	0.55391	0.26327	0.91001	0.29796
0.15	0.72768	0.59723	0.27887	0.91110	0.32491
0.16	0.69271	0.62653	0.28429	0.90501	0.31924

Fig. 1 *– ROC curves based on the improved Framingham model (SG continuous FRS+) compared to the Singapore adapted continuous Framingham Risk Score (SG continuous FRS) alone. Both curves are based on logistic regression models using the SG continuous FRS with and without the additional variables incorporated (Glucose, DBP, lnDailySteps, Resting_HR). AUC indicates area under curve.*





Predicted probability of high calcium score and risk of myocardial infarction

Logistic regression myocardial infarction linear predictor:

y = - 23.9046 + 0.0527·Age + 0.2774·Gender(M=1, F=0) – 0.00282·SBP + 0.1705·Cholesterol_Total + 1.1040·Cholesterol_HDL + 0.4671·Smoking(Previously=1, Yes/No=0) – 0.1120·Smoking (Yes=1, Previously/No=0) + 0.5548·Glucose + 0.0349·DBP + 0.0498·Resting_HR + 0.8632·*ln*DailySteps

Predicted probability of myocardial infarction: $p = e^y/(1 + e^y)$

Predicted probability Agatston ≥ 75th percentile	Sensitivity	Specificity	PPV	NPV	Youden Index
0.09	0.90625	0.40954	0.24426	0.95399	0.31579
0.10	0.86393	0.45984	0.25196	**0.94166**	0.32377
0.11	0.83807	0.51196	0.26556	0.93759	0.35003
0.12	0.82813	0.54441	0.27682	0.93766	0.37253
0.13	0.82500	0.57664	0.29096	0.93995	0.40164
0.14	0.78613	0.61123	0.29875	0.93140	0.39736
0.15	0.75426	0.64892	0.31133	0.92627	0.40318
0.16	0.70313	0.66118	0.30406	0.91364	0.36431

Fig. 2 *– ROC curves based on the improved and recalibrated Framingham model (SG continuous FRS++) compared to the Singapore adapted continuous Framingham Risk Score (SG continuous FRS) alone. Both curves are based on logistic regression models using variables from the SG continuous FRS (Age, Gender, SBP, Cholesterol_Total, Cholesterol_HDL, Smoking) with and without the additional variables incorporated (Glucose, DBP, lnDailySteps, Resting_HR). AUC indicates area under curve.*

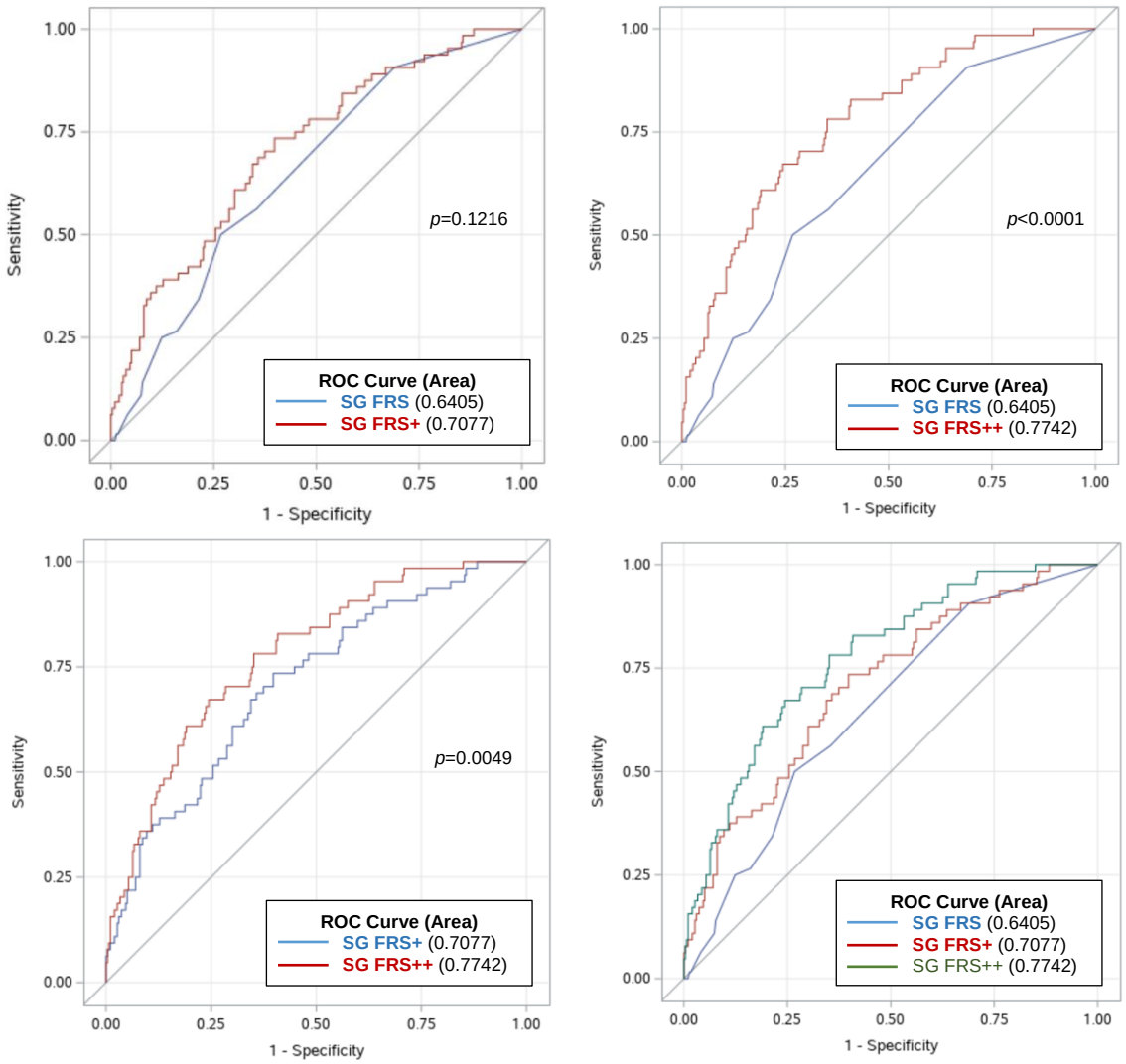
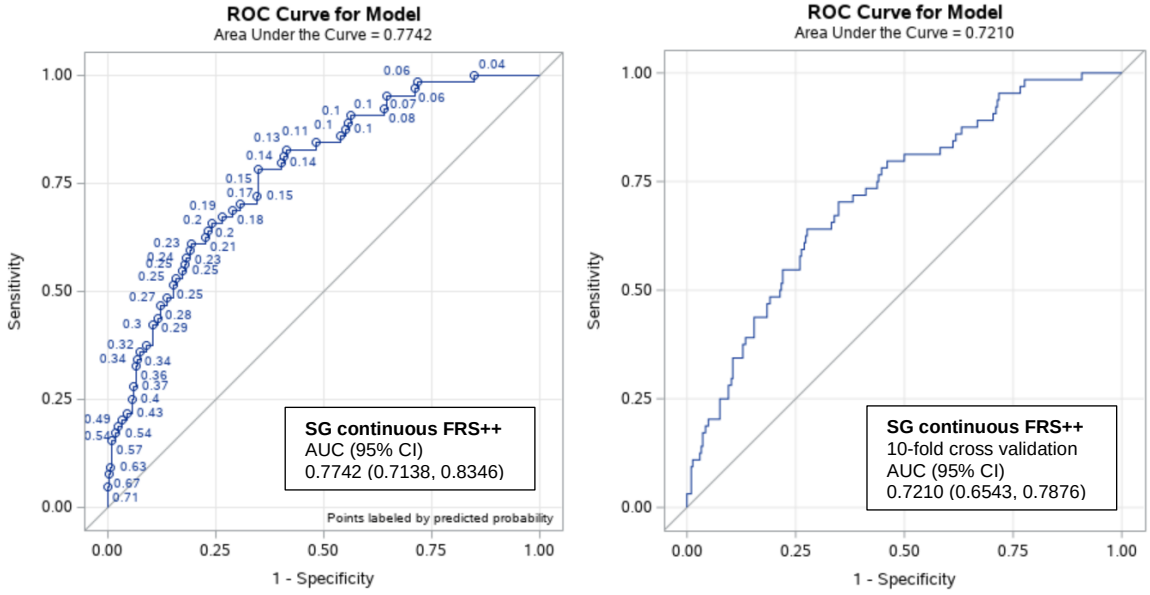
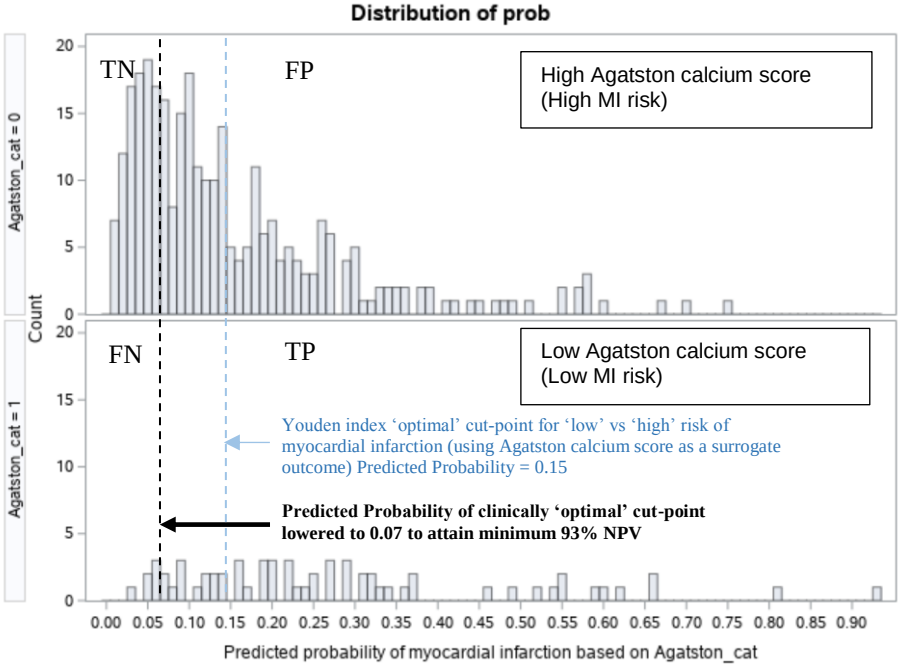


Fig. 3 *– ROC curves based on the improved and recalibrated Framingham model (SG continuous FRS++), and the improved Framingham model (SG continuous FRS+) were compared to the Singapore adapted continuous Framingham Risk Score (SG continuous FRS). All ROC curves are based on logistic regression models using variables from the SG continuous FRS (Age, Gender, SBP, Cholesterol_Total, Cholesterol_HDL, Smoking), with and without the additional variables incorporated (Glucose, DBP, lnDailySteps, Resting_HR), and with recalibration of existing variables (Age, Gender, SBP, Cholesterol_Total, Cholesterol_HDL, Smoking). AUC indicates area under curve. Statistically significant differences were found between the AUC of the SG FRS and SG FRS++, but no significant differences were found between the AUC of the SG FRS and SG FRS+. All p-values were two sided and statistically significant for p<0.05.*





Predicted probability Agatston ≥ 75th percentile	Sensitivity	Specificity	PPV	NPV	Youden Index
0.06	0.94370	0.26935	0.21384	0.95831	0.21305
0.07	0.88739	0.32000	0.21553	**0.93092**	0.20739
0.08	0.87144	0.36111	0.22312	0.93034	0.23256
0.09	0.83417	0.39767	0.22578	0.91942	0.23183
0.10	0.81300	0.45233	0.23812	0.91964	0.26533
0.11	0.80500	0.50000	0.25311	0.92403	0.30500
0.12	0.79033	0.53642	0.26419	0.92400	0.32675
0.13	0.74467	0.56642	0.26557	0.91340	0.31108
0.14	0.71688	0.60650	0.27732	0.91051	0.32338
0.15	0.70300	0.63820	0.29035	0.91079	0.34120
0.16	0.68314	0.65357	0.29337	0.90740	0.33671

Fig. 4 *– 10-fold cross validation analysis ROC curve based on the improved and recalibrated Framingham model (SG continuous FRS++). The curve is based on logistic regression models using variables from the SG continuous FRS (Age, Gender, SBP, Cholesterol_Total, Cholesterol_HDL, Smoking) with and without the additional variables incorporated (Glucose, DBP, lnDailySteps, Resting_HR). AUC indicates area under curve.*